111-1,120.00

#37

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. 4,738,974**
Issued:	**April 19, 1988**
To:	**Arne E. Brändström**
For:	**Base Addition Salts of Omeprazole**

Date of Hand-Delivery April 19, 2001.
I hereby certify that this paper is being hand-delivered on the date indicated above and is addressed to the:
Assistant Commissioner for Patents
Washington, D.C. 20231.

CAROL B. POTTS
Name of person delivering by hand the paper and fee

Carol B. Potts
Signature of person delivering by hand the paper and fee

Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

TABLE OF CONTENTS

EXHIBITS

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicant, Aktiebolaget Hässle ("AB Hässle"), a corporation organized and existing under the laws of Sweden, the address of which is S-431 83 Mölndal, Sweden, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 4,738,974, granted to Arne E. Brändström on the 19th day of April, 1988, for BASE ADDITION SALTS OF OMEPRAZOLE by virtue of an assignment recorded March 5, 1984, at Reel 4258, Frame 0076.

Applicant AB Hässle and AstraZeneca LP, the holder of the marketing approval for Nexium™ Delayed-Release Capsules, the Approved Product that is relevant to this application, are both owned by AstraZeneca, headquartered in London, England. AstraZeneca was formed in April 1999 from the merger of Astra AB with Zeneca Group PLC.

Applicant, through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the statute and by the Rules of Practice in Patent Cases, 37 C.F.R. § 1.740. For the convenience of the United States Patent and Trademark Office, the information in this application is presented in the order set forth in Section 1.740 of the Rules.

1. Identity of the Approved Product (37 C.F.R. § 1.740(a)(1))

Pursuant to 37 C.F.R. § 1.740, the chemical and generic name, physical structure or characteristics of the Approved Product, Nexium™ Delayed-Release Capsules, are as follows:

Nexium™ Delayed-Release Capsules contain, as the active ingredient, esomeprazole magnesium, which is the magnesium salt of the S-isomer of omeprazole and the chemical

name of which is bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate.

2. Identity of Federal Statute Under Which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2))

The Approved Product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355(b)).

3. Identity of Date on Which Approved Product Received Permission for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(3))

The Approved Product received permission for commercial marketing or use in a letter dated February 20, 2001, from Lilia Talarico, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III, and Mark J. Goldberger, M.D., M.P.H., Director, Division of Special Pathogen and Immunologic Drug Products, Office of Drug Evaluation IV, both of the Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

4. Identity of Active Ingredient (37 C.F.R. § 1.740(a)(4))

Applicant avers that the active ingredient of the Approved Product is esomeprazole magnesium, which has not previously been approved for commercial marketing or use under the FDCA, 21 U.S.C. § 355(b). Please note that esomeprazole magnesium is a different active ingredient from omeprazole, which is marketed as Prilosec® (NDA 019810), for which a patent term extension has previously been granted.

5. Timely Filing of This Application (37 C.F.R. § 1.740(a)(5))

This application is filed, pursuant to 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f), within the permitted sixty-day (60-day) period that began on February 20, 2001, the date the product received permission under 21 U.S.C. § 355(b), and that will expire on April 20, 2001.

6. Identity of the Patent for Which an Extension Is Sought (37 C.F.R. § 1.740(a)(6))

Inventor:	**Arne E. Brändström**
Patent No.:	**4,738,974**
Issued:	**April 19, 1988**
Expiration:	**April 19, 2005**

7. Copy of Patent Attached (37 C.F.R. § 1.740(a)(7))

A copy of the patent for which an extension is being sought, including the entire specification (with claims) and drawings, is attached as Exhibit A.

8. Disclaimers, Certificates of Correction, Receipts of Maintenance Fee Payment or Reexamination Certificate (37 C.F.R. § 1.740(a)(8))

Documentation of maintenance fee payments for pay years 04, 08, and 12 is attached as Exhibit B. No disclaimer, certificate of correction or reexamination certificate has been issued with respect to the patent.

9. Statement of Patent Claim Coverage of Approved Product (37 C.F.R. § 1.740(a)(9))

U.S. Patent No. 4,738,974 claims the Approved Product, as shown in Exhibit C. Exhibit C presents a chart showing each applicable patent claim (claims 1-2, 4-6, 8-10, 12-14, 16-18 and 20) and the manner in which each such applicable patent claim reads on the Approved Product or method of using the Approved Product.

10. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) (37 C.F.R. § 1.740(a)(10))

Two NDAs, NDA 21-153 and NDA 21-154, were submitted and approved for Nexium™ Delayed-Release Capsules. The relevant dates are as follows:

a. Dates Relating to NDA 21-153

a. Effective Date of the Investigational New Drug (IND) Application: August 18, 1997

b. IND Number: 53,733

c. Date on which the NDA was initially submitted: December 3, 1999

d. NDA Number: 21-153

e. Date on which the NDA was approved: February 20, 2001

b. Dates Relating to NDA 21-154

a. Effective Date of the Investigational New Drug (IND) Application: December 21, 1997

b. IND Number: 54,599

c. Date on which the NDA was initially submitted: February 28, 2000

d. NDA Number: 21-154

e. Date on which the NDA was approved: February 20, 2001

11. Brief Description of Significant Activities Undertaken by Marketing Applicant During Applicable Regulatory Review Period and Respective Dates (37 C.F.R. § 1.740(a)(11))

Attached as Exhibit D is a brief description of the significant activities undertaken by the marketing applicant, AstraZeneca LP, with respect to Nexium™ Delayed-Release Capsules during the regulatory review period for each of the two NDAs approved: (a) NDA 21-153, July 18, 1997, to February 20, 2001; and (b) NDA 21-154, November 21, 1997, to February 20, 2001.

12. Statement of Eligibility for Extension (37 C.F.R. § 1.740(a)(12))

Applicant believes that U.S. Patent No. 4,738,974 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. § 156(a), 37 C.F.R. § 1.710

U.S. Patent No. 4,738,974 claims a product and a method of using a product.

b. 35 U.S.C. § 156(a)(1)

The term of U.S. Patent No. 4,738,974 will not have expired before submission of this application.

c. 35 U.S.C. § 156(a)(2)

The term of U.S. Patent No. 4,738,974 has never been extended under 35 U.S.C. § 156(e)(1).

d. 35 U.S.C. § 156(a)(3)

This application for extension is submitted by the owner of record in accordance with the requirements of 35 U.S.C. § 156(d)(1)-(4) and rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. § 156(a)(4)

The Approved Product, Nexium™ Delayed-Release Capsules, has been subjected to a regulatory review period before its commercial marketing or use.

f. 35 U.S.C. § 156(a)(5)(A)

The commercial marketing or use of the Approved Product, Nexium™ Delayed-Release Capsules is the first permitted commercial marketing or use of the product under the FDCA (21 U.S.C. § 355(b)) under which such regulatory review period occurred.

g. 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory review period for the Approved Product, Nexium™ Delayed-Release Capsules.

13. Statement as to Length of Extension Claimed and the Determination of Such Extension (37 C.F.R. § 1.740(a)(12))

In the opinion of the Applicant, U.S. Patent No. 4,738,974 is entitled to an extension of 865 days, pursuant to 35 U.S.C. § 156 and the implementing regulations, based upon the regulatory review period pertaining to NDA 21-153 for Nexium™ Delayed-Release Capsules.

Two NDAs, NDA 21-153 and NDA 21-154, have been approved for Nexium™ Delayed-Release Capsules. The regulatory review periods for NDAs 21-153 and 21-154 began on August 18, 1997, and December 21, 1997, respectively, but both were approved on February 20, 2001. Accordingly, the regulatory review period pertaining to NDA 21-153 is longer than the regulatory review period pertaining to NDA 21-154. All else being equal between the two NDAs, Applicant claims a length of extension of 865 days based upon the regulatory review period pertaining to NDA 21-153. Only as a subordinate claim for extension is the regulatory review period for NDA 21-154 set forth below.

a. Primary Claim for Extension of [865] Days Based Upon the Regulatory Review Period Pertaining to NDA 21-153

The claimed length of this extension of 865 days pertaining to NDA 21-153 was determined pursuant to 37 C.F.R. § 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. § 156(g)(1)(B), which began on August 18, 1997, and ended on February 20, 2001, and lasted 1284 days, the sum of computations in (a) and (b) below:

(a) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on August 18, 1997, and ended on December 3, 1999, a period of 838 days; and

(b) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on December 3, 1999, and ended on February 20, 2001, a period of 446 days;

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 13(a)(1) above (1284 days) less

(a) The number of days in the regulatory review period which were on or before the date on which the patent issued, April 19, 1988, which is zero (0) days, and

(b) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(c) One-half the number of days determined in subparagraph (13)(a)(1)(a) (838) after subtracting (13)(a)(2)(a) and (b) (0), or 419 days, which leaves 865 days;

(3) The number of days as determined in subparagraph 13(a)(2) in its entirety, (865) days, when added to the original term of the patent, would result in the date September 1, 2007;

(4) Fourteen (14) years when added to the date of approval (February 20, 2001) would result in the date February 20, 2015;

(5) The earlier date as determined in subparagraphs (13)(a)(3) and (13)(a)(4) is September 1, 2007;

(6) Since the original patent issued after September 24, 1984, five (5) years are added to the original expiration date of the patent, resulting in a date of April 19, 2010; and

(7) The earlier of the dates obtained in paragraph 13(a)(5) and in paragraph 13(a)(6) is September 1, 2007.

Therefore, the length of extension of patent term claimed by applicant is 865 days, which is the period of time needed to extend the original expiration of term until September 1, 2007.

b. Subordinate Claim for Extension Based Upon the Regulatory Review Period Pertaining to NDA 21-154

For its secondary claim for extension that is to be considered subordinate to the main claim set forth above in paragraph 13(a) for NDA 21-153, Applicant sets forth the length of this extension of 759 days pertaining to NDA 21-154, which was determined pursuant to 37 C.F.R. § 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. § 156(g)(1)(B), which began on December 21, 1997, and ended on February 20, 2001, and lasted 1159 days, the sum of computations in (a) and (b) below:

(a) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on December 21, 1997, and ended on February 28, 2000, a period of 800 days; and

(b) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on February 28, 2000, and ended on February 20, 2001, a period of 359 days;

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 13(b)(1) above (1159 days) less

(a) The number of days in the regulatory review period which were on or before the date on which the patent issued, April 19, 1988, which is zero (0) days, and

(b) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(c) One-half the number of days determined in subparagraph (13)(b)(1)(a) (800) after subtracting 13(b)((2)(a) and (b) (0), or 400 days, which leaves 759 days;

(3) The number of days as determined in subparagraph 13(b)(2) in its entirety (759), when added to the original term of the patent, would result in the date May 18, 2007;

(4) Fourteen (14) years when added to the date of approval (February 20, 2001) would result in the date February 20, 2015;

(5) The earlier date as determined in subparagraphs (13)(b)(3) and (13)(b)(4) is May 18, 2007;

(6) Since the original patent issued after September 24, 1984, five (5) years are added to the original expiration date of the patent, resulting in a date of April 19, 2010; and

(7) The earlier of the dates obtained in paragraph 13(b)(5) and in paragraph 13(b)(6) is May 18, 2007.

Accordingly, for its subordinate claim based on NDA 21-154, Applicant has set forth the determination of the length of extension of patent term of 759 days, which is the period of time needed to extend the original expiration of term until May 18, 2007]. Applicant only submits the information pertaining to NDA 21-154 to comply with the requirements for application for patent term extension and again states that it is of the opinion that it is entitled to an extension of 865 days based upon the longer regulatory review period pertaining to NDA 21-153.

14. Statement of Acknowledgment of Duty to Disclose Material Information (37 C.F.R. § 1.740(a)(13))

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in this application.

15. Prescribed Fee (37 C.F.R. § 1.740(a)(14))

A check in the amount of $1,120.00, as prescribed in 37 C.F.R. § 1.20(j), is enclosed. Any additional necessary fees may be charged to Deposit Account 23-1703.

16. Contact Information (37 C.F.R. § 1.740(a)(15))

All inquiries and correspondence relating to this application for patent term extension should be directed to:

Leslie Morioka
Patent Department
White & Case
1155 Avenue of the Americas
New York, NY 10036-2787
Tel.: (212) 819-8200
Fax: (212) 354-8113

Anna Brodowsky, Esq.
AstraZeneca AB
R&D Headquarters
Global Intellectual Property
S-151 85 Södertälje
Sweden
Tel: 011-46-8-553-260-00
Fax: 011-46-8-553-288-20

17. Copies Enclosed (37 C.F.R. § 1.740(a)(16))

Four duplicate copies of the present application papers are enclosed. The undersigned patent attorney certifies under penalty of perjury that the attached duplicates of the application papers are true and correct copies of such papers.

Respectfully submitted,

Dated: April 18, 2001

Leslie Morioka
Reg. No. 40,304

Attorney for Applicant

WHITE & CASE
1155 Avenue of the Americas
New York, New York 10036
Tel.: (212) 819-8200
Fax: (212) 354-8113

United States Patent [19]

Brändström

[11] **Patent Number: 4,738,974**

[45] **Date of Patent: Apr. 19, 1988**

[54] **BASE ADDITION SALTS OF OMEPRAZOLE**

[75] Inventor: **Arne E. Brändström**, Gothenburg, Sweden

[73] Assignee: **Aktiebolaget Hassle**, Sweden

[21] Appl. No.: **854,739**

[22] Filed: **Apr. 21, 1986**

Related U.S. Application Data

[63] Continuation of Ser. No. 640,020, Aug. 10, 1984, abandoned, which is a continuation-in-part of Ser. No. 586,107, Mar. 5, 1984, abandoned.

[51] **Int. Cl.**[4] **C07D 401/12; A61K 31/44**

[52] **U.S. Cl.** **514/338; 546/271**

[58] **Field of Search** 546/271; 514/338

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,045,563	8/1977	Berntsson et al.	546/271
4,045,564	8/1977	Berntsson et al.	546/271
4,323,567	4/1982	Narisada et al.	544/90
4,472,409	9/1984	Senn-Bilfinger	546/271

FOREIGN PATENT DOCUMENTS

0005129	10/1979	European Pat. Off. .
0045200	2/1982	European Pat. Off. .
1234058	6/1971	United Kingdom .

OTHER PUBLICATIONS

The Theory of Organic Chemistry, An Advanced Course, by Gerald E. K. Branch, Ph.D and Melvin Calvin, Ph.D, Prentice-Hall, Inc. (1946).

Heterocyclic Compounds, vol. 5, Five-Membered Heterocycles Containing Two Hetero Atoms and Their Benzo Derivatives, edited by Robert C. Elderfield, John Wiley & Sons, Inc. (1952).

Derwent, 17863E (abstract).

K. A. Connors, G. L. Amidon and V. J. Stella: "Chemical Stability of Pharmaceuticals", second edition, John Wiley & Sons, New York, 1986, chapters 5 and 6.

J. T. Carstensen: "Pharmaceutics of Solids and Solid Dosage Forms", John Wiley & Sons, New York, 1977, chapter VII.

J. Tingstad and J. Dudzinski: "Preformulation Studies II: Stability of Drug Substances in Solid Pharmaceutical Systems", *J. Pharm. Sci.*, 62, 1973, 1856–1860.

S. M. Berge, L. D. Bighley and D. C. Monkhouse: "Pharmaceutical Salts", *J. Pharm. Sci.*, 66, 1977, 1–19.

H. V. Maulding, M. A. Zoglio, F. E. Pigois and M. Wagner: "Pharmaceutical Heterogeneous Systems IV: A Kinetic Approach to the Stability Screening of Solid Dosage Forms Containing Aspirin", *J. Pharm. Sci.*, 58, 1969, 1359–1362.

C. A. Kelly: "Determination of the Decomposition of Aspirin", *J. Pharm. Sci.*, 59, 1970, 1053–1079.

E. De Ritter, L. Magid, M. Osadca and S. H. Rubin: "Effect of Silica Gel in Stability and Biological Availability of Ascorbic Acid", *J. Pharm. Sci.*, 59, 1970, 229–232.

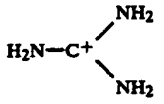
"Draft Guideline for Stability Studies for Human Drugs and Biologics", Mar. 1984, pp. 1–25.

Primary Examiner—Jane T. Fan

Attorney, Agent, or Firm—Brumbaugh, Graves, Donohue & Raymond

[57] **ABSTRACT**

Novel salts of omeprazole with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



as cation; processes for their preparation thereof, pharmaceutical compositions containing such salts and their use in medicine.

20 Claims, No Drawings

BASE ADDITION SALTS OF OMEPRAZOLE

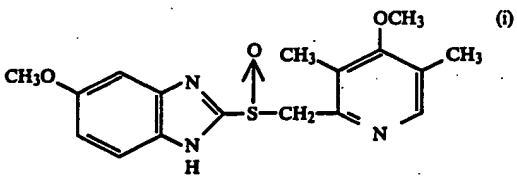
This application is a continuation of application Ser. No. 640,020, filed on 8/10/84, now abandoned, which is a continuation-in-part of application Ser. No. 586,107, filed on Mar. 5, 1984, now abandoned.

FIELD OF THE INVENTION

The invention relates to novel salts of the known compound omeprazole.

BACKGROUND OF THE INVENTION

The compound known under the generic name omeprazole, having the structural formula



(i)

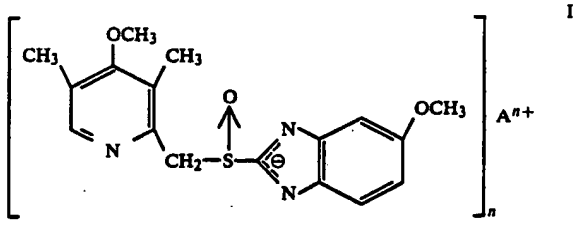
which is described i.a. in European patent specification 0005129, is being extensively investigated clinically as a gastric acid secretion inhibiting agent.

Omeprazole is useful for inhibiting gastric acid secretion as well as for providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, omeprazole may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, omeprazole may be used for prevention and treatment of other gastrointestinal disorders where cytoprotective and/or gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive alcohol consumption.

The term "omeprazole" as used in this specification designates the neutral form of the compound of the formula (i), that is the form as given in the formula (i) without salt forming components present. A problem with omeprazole is its stability characteristics. Upon storage without any special precautions being taken, it is degraded at a rate which is higher than desired. A storage during accelerated conditions, that is at +37° C. and at a relative humidity of 80% for a period of 6 months, about 6% of the substance is converted to degradation products. While the rate of decomposition of omeprazole at normal storage conditions is lower, it is nevertheless desirable to obtain physical forms of omeprazole which exhibit improved stability. This need for more stable forms of omeprazole is apparent when considering the often considerable time periods involved from the synthesis of the active substance through its incorporation in pharmaceutical preparations, distribution of the finished product to pharmacies etc. up to the consumption of the preparation by the patient. The present invention provides such new forms of omeprazole which exhibit improved storage stability.

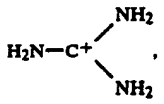
THE INVENTION

It has been found that the novel alkaline salts of omeprazole with the structural formula



I

wherein n is 1,2, or 4; A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



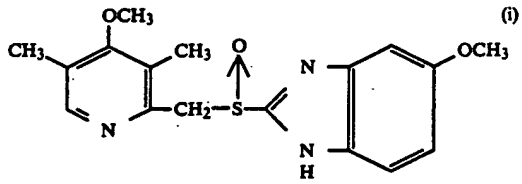
wherein R^1 is an alkyl group containing 1–4 carbon atoms are more stable during storage than the corresponding neutral form of omeprazole. The salts of the formula I are also easier to handle than the neutral form in the manufacture of pharmaceutical dosage units.

A preferred group of omeprazole salts of the formula I are those wherein A^{n+} is Na^+, K^+, Mg^{2+} and Ca^{2+}.

Further preferred salts are those wherein A^{n+} is Na^+, Mg^{2+} and Ca^{2+}. The Na^+-salt is especially preferred for the preparation of liquid pharmaceutical formulations, e.g. solutions for intravenous administration. The Mg^{2+} and Ca^{2+} salts are especially preferred for the preparation of tablets. The Mg^{2+} salt is particularly preferred.

Illustrative examples of the alkyl group R^1 are CH_3, C_2H_5, n-C_3H_7, and n-C_4H_9.

The novel salts I of the invention are prepared by reacting omeprazole of the formula

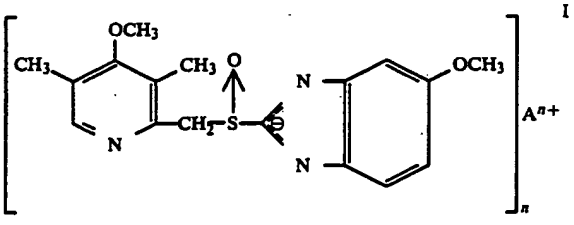


(i)

with a base capable of releasing the cation

A^{n+} (ii)

wherein A^{n+} is as defined above,
to give a salt of the formula



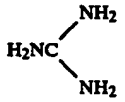
I

which salt is thereafter isolated.

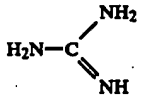
Examples of bases capable of releasing the cation A^{n+}, and examples of reaction conditions are given below.

(a) Salts of the formula I wherein A is Li, Na or K are prepared by treating omeprazole with LiOH, NaOH or KOH in an aqueous or nonaqueous medium or with LiOR, $LiNH_2$, $LiNR_2$, NaOR, $NaNH_2$, $NaNR_2$, KOR, KNH_2 or KNR_2, wherein R is an alkyl group containing 1–4 carbon atoms, in a nonaqueous medium.

(b) Salts of the formula I wherein A is Mg, Ca, or Ti are prepared by treating omeprazole with $Mg(OR)_2$, $Ca(OR)_2$, CaH_2, $Ti(OR)_4$ or TiH_4, wherein R is an alkyl group containing 1–4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. (c) Salts of the formula I wherein A is



are prepared by treating omeprazole with the strong base



dissolved in a solvent, for example an alcohol.

(d) A salt of formula I may be converted to another salt of the same formula by exchanging the cation. When both the starting material and the salt obtained as final product are sufficiently soluble, such an exchange may be performed by using a cation-exchange resin saturated with the cation desired in the product. The exchange may also be performed by utilizing the low solubility of a desired salt. By this principle, for example, Na^+ as a counter ion may be exchanged for Ca^{2+} or Mg^{2+}.

(e) The reaction between the compounds (i) and (ii) may also be carried out by ion-pair extraction. For example, tetrabutylammonium salts of the invention may be prepared by dissolving the Na^+-salt in water containing tetrabutylammonium sulfate followed by extraction of the tetrabutylammonium salt I into a methylene chloride phase, and subsequent isolation of the tetrabutylammonium salt I. In this manner also other tetraalkylammonium salts I may be prepared.

Illustrative examples of the radical R are CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_4H_9, sec.-C_4H_9 and tert.-C_4H_9.

The invention also relates to pharmaceutical compositions containing a novel salt of omeprazole as active ingredient; to the use of the novel omeprazolesalts for providing local gastrointestinal cytoprotective effects in mammals and man; to the use of the novel omeprazole salts in the prevention and treatment of gastrointestinal inflammatory diseases in mammals and man; to the use of the novel omeprazole salts for inhibiting gastric acid secretion in mammals and man; to a method for inhibiting gastric acid secretion in mammals and man by administering a compound of the formula I; to a method for the treatment of gastrointestinal inflammatory diseases in mammals and man by administering a compound of the formula I; and to a method for providing gastrointestinal cytoprotective effects in mammals and man by orally administering a compound of the formula I.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration; however only oral administration is suitable for providing gastrointestinal cytoprotective effects. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further aspect of the invention. Usually the amount of active compound is between 0.1–95% by weight of the preparation, between 0.2–20% by weight in preparations for parenteral use and between 1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, e.g. lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. Since the compounds of the invention are susceptible to degradation in acid to neutral media, the above-mentioned granules or tablets when used for gastric acid inhibition are preferably coated with an enteric coating which protects the active compound from acid degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules are preferably enteric coated as described above. Hard gelatine capsules may contain enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier e.g. lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine; the hard gelatine capsules are preferably enteric coated as described above. In orally administering the compounds of the invention to provide gastrointestinal cytoprotective effects in mammals and man non-enteric coated oral dosage forms are usually preferred, however in order to achieve intestinal cytoprotection enteric coated dosage forms may be needed.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation

to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose and thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilising agents and/or buffering agents and may be manufactured in unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use. Sodium salts of the invention are preferably used in the preparation of parenteral formulations.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the manner of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 400 mg per day of active substance.

The following examples will further illustrate the invention.

EXAMPLE 1

Preparation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium salt (omeprazole sodium salt)

Omeprazole (1000 g, 2.90 mol) was added to a solution of NaOH (116 g, 2.90 mol) in deionized water (25 L). After stirring for 5 min methylene chloride (5 L) was added and stirring was continued for 10 min. The two phases were separated. The aqueous phase was washed with methylene chloride (5 L), filtered clear (Celite) and concentrated by evaporation under reduced pressure to about 2 L total volume. Absolute ethanol (6 L) was added and the evaporation was continued until dryness. Ethyl acetate (7 L) was added, the mixture was stirred under reflux for 30 min. After cooling and standing over night the resulting slurry was stirred with an additional amount (2 L) of ethyl acetate and filtered. The filter cake was washed with diethyl ether and dried under reduced pressure at 40° C. over night giving omeprazole sodium salt (975 g, 92%), mp 208°-210° C., NMR: $\delta(D_2O)$: 1.85(s, 3H), 2.1(s, 3H), 3.5(s, 3H), 3.85(s, 3H), 4.75(s, 2H), 6.85(dd, 1H), 7.2(d, 1H), 7.55(d, 1H), 8.15(d, 1H).

EXAMPLE 2

Preparation of omeprazole sodium salt

Omeprazole (1300 g, 3.77 mol) was added under vigorous mechanic stirring to a mixture of tetrahydrofuran (13 L) and 50% aqueous NaOH (296 g, 3.7 mol) and stirring was then continued for 45 min. Trichloroethylene (5.7 L) was added and stirring was continued over night at room temperature. The mixture was cooled to +5° C. and then stirred for 3 h. The precipitate was filtered off and the filter cake was washed with trichloroethylene (5 L) and dried under reduced pressure at 50° C. giving omeprazole sodium salt (1314 g, 95%), mp 208°-210° C.

EXAMPLE 3

Preparation of omeprazole potassium salt

Omeprazole (10.0 g, 0.0290 mol) was added to a solution of KOH (1.60 g, 0.0285 mol) in deionized water and then methylene chloride (50 ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (50 ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline residue. Recrystallization from ethyl acetate yielded omeprazole potassium salt, mp. 148°-150° C. (soluble in water).

EXAMPLE 4

Preparation of di-omeprazole calcium salt dihydrate

Anhydrous $CaCl_2$ (17.9 g, 0.161 mol) dissolved in deionized water (200 ml) was added dropwise under viogorous stirring to a solution of omeprazole sodium salt (125 g, 0.340 mole) in deionized water (1250 ml) and then stirring was continued for 1 h at room temperature. The precipitate was centrifuged down and washed with deionized water until no Cl^- was detectable ($AgNO_3$). After drying in the air and grinding, the crystals were dried in vacuum at 40° for 20 h yielding omeprazole calcium salt dihydrate (104 mg, 80%), mp 182°-184° C., NMR: $\delta(CDCl_3$1 drop of DMSO-d_6) 2.0(s, 3H), 2.15(s, 3H), 3.6(s, 3H), 3.7(s, 3H), 4.5(s, 2H), 6.7(dd, 1H), 7.1(d, 1H), 7.6(d, 1H, 8.15(s, 1H).

EXAMPLE 5

Preparation of di-omeprazole magnesium salt dihydrate

Anhydrous $MgCl_2$ (16.2 g, 0.17 mol) dissolved in deionized watr (625 ml) was added dropwise under vigorous stirring to a solution of omeprazole sodium salt (125 g, 0.340 mol) in deionized water (1560 ml) and then the stirring was continued for 1 h at room temperature. The precipitate was centrifugated down and then washed with deionized water until no Cl^- was detectable ($AgNO_3$). Drying in the air, grinding and drying in vacuum at 40° for 24 h yielded omeprazole magnesium salt dihydrate (111 g, 87%) mp 177°-178° C.

EXAMPLE 6

Preparation of di-omeprazole magnesium salt

Magnesium (0.35 g, 0.0145 mol) was reacted with absolute methanol (10 ml) (in the presence of one drop of CCl_4) to give a solution of $Mg(OCH_3)_2$ in methanol solution. More methanol (10 ml) was added and the solution was added dropwise to a solution of omeprazole (10 g, 0.029 m) in methanol (200 ml) and the mixture was then stirred for 30 min at room temperature. Evaporation gave a crystalline solid of the di-omeprazole magnesium salt, mp. 178°-180°.

EXAMPLE 7

Preparation of omeprazole tetrabutylammonium salt

Omeprazole sodium salt (3.8 g, 0.010 mol) was added to a mixture of tetrabutylammonium hydrogensulphate (3.5 g, 0.010 mol) and NaOH (0.42 g, 0.0105 mol) in deionized water (15 ml). Methylene chloride (10 ml) was added and the mixture was shaken in a separatory

funnel. After separation of the phases the organic phase was dried and the solvent evaporated off giving omeprazole tetrabutylammonium salt (3.5 g, 60%), NMR: δ($CDCl_3$): 0.8–1.15(m, 12H), 1.15–1.6(m, 16H), 2.25(s, 3H), 2.3(s, 3H), 2.75–3.15(m, 8H), 3.75(s, 3H), 3.9(s, 3H), 4.7(d, 1H), 5.05(d, 1H), 6.8(dd, 1H), 7.3(d, 1H), 7.7(d, 1H), 8.35(s, 1H).

EXAMPLE 8

Preparation of omeprazole guanidinium [$C^+(NH_2)_3$] salt

A solution of guanidine (0.0029 mol) [prepared from guanidinium nitrate and KOH] in ethanol (50 ml) was added to a solution of omeprazole (1.0 g, 0.0029 mol) and the resulting solution was stirred for 15 min. The solvent was evaporated giving omeprazole guanidinium salt, mp 110°–112° C. (soluble in water).

EXAMPLE 9

Preparation of tetra-omeprazole titanium salt

Titanium tetraisopropylate (1.03 g, 0.0036 mol) was added to a solution of omeprazole in dry isopropanol (250 ml) and the mixture was stirred under N_2 at room temperature for 4 h. (A white precipitate was formed). Evaporation of the solvent followed by washing 3 times with light petroleum and drying in vacuum gave a white crystalline powder of tetraomeprazole titanium salt, mp >260° C.

EXAMPLE 10

Preparation of omeprazole litium salt

Omeprazole (3.0 g, 0.0087 mol) was added to a solution of LiOH (0.207 g, 0.00865 mol) in deionized water and then methylene chloride (25 ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (25 ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline omeprazole litium salt, mp. 198°–200° C. (soluble in water).

NMR: δ($CDCl_3$) 1.65 (s, 3H), 1.8 (s, 3H), 3.45 (s, 3H), 3.4 (s, 3H), 4.2 (s, 2H), 6.6 (dd, 1H), 6.95 (d, 1H), 7.45 (d, 1H), 7.75 (s, 1H).

The NMR data given in the examples are measured at 90 MHz.

Incorporation of the novel omeprazole salts of the present invention in pharmaceutical preparations is exemplified in the following examples.

EXAMPLE 11

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

I	Omeprazole sodium salt	1.0 g
	Sugar, powder	30.0 g
II	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05 g
	Ethanol	5.0 g
	Sorbic acid	0.5 g
	Sodium dihydrogen phosphate q.s. to pH=	9.0 g
	Distilled water q.s. to a final volume of	100 ml

I Powdered omeprazole sodium salt was carefully dry mixed with powdered sugar, dried in a vacuum oven over-night and dispensed into bottles each containing 31.0 gram of the powder mixture.

II A solution of saccharine, glycerol, flavouring agent, ethanol, sodium dihydrogen phosphate, sorbic acid and water was prepared, and dispensed into vials. When mixed with the powder mixture of omeprazole sodium salt and sugar the final volume was 100 ml.

Solvent vial II is to be added to powder mixture vial I just prior to use. The formed suspension is stable for ten days when stored at refrigerator temperature.

The salt given above may be replaced with another salt of the invention.

EXAMPLE 12

Enteric-coated tablets

An enteric-coated tablet containing 20 mg of active compound was prepared from the following ingredients:

I	Omeprazole magnesium salt	200 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Omeprazole magnesium salt, powder, was mixed with lactose, and granulated with a water solution of methyl cellulose. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tabletting machine using 6 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota ®, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

EXAMPLE 13

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

I	Omeprazole sodium salt	4.26 g
	Sterile water	200 ml
II	Polyethylene glycol 400 for injection	400 g
	Sodium dihydrogen phosphate	1.5 g
	Sterile water to a final volume of	1000 ml

I Omeprazole sodium salt 4.26 g, corresponding to 4.0 g of omeprazole, was dissolved in sterile water to a final volume of 200 ml. The solution was filtered through a 0.22μ filter and dispensed into sterile vials, each vial containing 2.0 ml. The vials were placed in a freeze drier with a shelf temperature of −40° C. When the solution in the vials had frozen, the solution was freeze dried. After drying the vials were stoppered.

II A solution of polyethylene glycol and sodium dihydrogen phosphate in sterile water was prepared, filtered through a 0.22μ filter, dispensed into sterile vials and the vials closed with a rubber stopper. The vials were sterilised in an autoclave at +120° C. for twenty minutes. Immediately before use 10.0 ml of solvent II is added to vial I. The clear solution contains 4 mg of omeprazole per milliliter.

TEST OF THE STABILITY OF OMEPRAZOLE SALTS OF THE INVENTION

The stability of omeprazole sodium salt, of the invention, obtained according to Example 1, was compared with the stability of the neutral form of omeprazole. Both test compounds were stored for six months at +37° C. and at a relative humidity of 80%. Thereafter,

the amount of degradation products which had formed was measured. The result is given in Table 1 below.

TABLE 1

Stability of neutral omeprazole and of omeprazole sodium salt after six months storage at +37° C. and 80% relative humidity	
Test compound	Amount of degradation products formed (percent calculated on original amount of omeprazole)
neutral omeprazole	6
omeprazole sodium salt	0.4

As seen in Table 1 the omeprazole sodium salt of the invention gave rise to substantially lower amounts of degradation products than the neutral form of omeprazole. This shows the improved stability of the novel omeprazole salts of the invention.

What I claim is:

1. A compound of the formula

[chemical structure]

wherein n is 1, 2, or 4; and A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, or Ca^{2+}.

2. A compound according to claim 1 wherein A^{n+} is Na^+, K^+, Mg^{2+} or Ca^{2+}.

3. A compound according to claim 1 wherein A^{n+} is Na^+.

4. A compound according to claim 1 wherein A^{n+} is Mg^{2+}.

5. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 1 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 2 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 3 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 4 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.

9. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 1 sufficient to inhibit gastric acid secretion.

10. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 2 sufficient to inhibit gastric acid secretion.

11. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 3 sufficient to inhibit gastric acid secretion.

12. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 4 sufficient to inhibit gastric acid secretion.

13. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 1 sufficient to treat gastrointestinal inflammatory disease.

14. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 2 sufficient to treat gastrointestinal inflammatory disease.

15. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 3 sufficient to treat gastrointestinal inflammatory disease.

16. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 4 sufficient to treat gastrointestinal inflammatory disease.

17. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 1 sufficient to provide gastrointestinal cytoprotective effects.

18. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 2 sufficient to provide gastrointestinal cytoprotective effects.

19. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 3 sufficient to provide gastrointestinal cytoprotective effects.

20. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 4 sufficient to provide gastrointestinal cytoprotective effects.

* * * * *

U.S. Patent and Trademark Office
OFFICE OF FINANCE

Return To USPTO Home Page
Finance Home Page

Maintenance Fee Statement

4738974

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMI ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURIN THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,738,974	185	3910	----	06/854,739	04/19/88	04/21/86	12	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	2599SA-PWC-A

Return to USPTO Home Page Return to Office of Finance Home Page

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

75N5/1020
BRUMBAUGH, GRAVES, DONOHUE & RAYMOND
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,738,974	184	1930	----	06/854,739	04/19/88	04/21/86	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	25995A-FWC-A

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

AS 1435 Ultra

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

25995-B-FWC

RECEIVED
BRUMBAUGH, GRAVES, DONOHUE & RAYMOND
'91 DEC -2 PM 12:33

BRUMBAUGH, GRAVES, DONOHUE & RAYMOND
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

DATE MAILED
11/21/91

TO--

183957

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,738,974	173	830	----	06/854,739	04/19/88	04/21/86	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

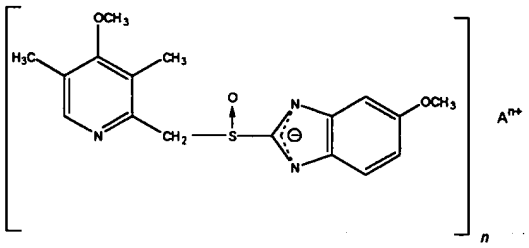
ITM NBR	ATTY DKT NUMBER
1	25995A-FWC-A

Trans to White & Case 6/89

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL 439 (rev 4 88)

PATENT CLAIM COVERAGE OF APPROVED PRODUCT

Applicable Claims of U.S. Patent No. 4,738,974	Manner in Which Each Claims Reads on Approved Product (Nexium™ Delayed-Release Capsules) or a Method of Using the Approved Product
1. A compound of the formula  wherein n is 1, 2, or 4; and A^{n+} is Li^{+}, Na^{+}, K^{+}, Mg^{2+}, or Ca^{2+}.	Claim 1 encompasses lithium, sodium, potassium, magnesium and calcium salts of (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole), which is the chemical name for racemic omeprazole. Racemic omeprazole comprises a mixture of optical isomers of omeprazole, including the S-isomer. Nexium™ Delayed-Release Capsules contain esomeprazole magnesium. Esomeprazole magnesium is the magnesium salt of the S-isomer of omeprazole. Esomeprazole magnesium is therefore a compound within the scope of claim 1.
2. A compound according to claim 1 wherein A^{n+} is Na^{+}, K^{+}, Mg^{2+} or Ca^{2+}.	Esomeprazole magnesium is a compound within the scope of claim 1 wherein A^{n+} is Mg^{2+}. Esomeprazole magnesium is therefore a compound within the scope of claim 2.
4. A compound according to claim 1 wherein A^{n+} is Mg^{2+}.	Esomeprazole magnesium is a compound within the scope of claim 1 wherein A^{n+} is Mg^{2+}. Esomeprazole magnesium is therefore a compound within the scope of claim 4.
5. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 1 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.	Each Nexium™ Delayed-Release Capsule comprises a pharmaceutical composition comprising 44.5 mg or 22.30 mg esomeprazole magnesium trihydrate (40 mg and 20 mg esomeprazole), a compound within the scope of claim 1 that is present in an amount that inhibits gastric acid secretion, and at least one pharmaceutically acceptable carrier. Nexium™ Delayed-Release Capsules are therefore within the scope of claim 5.
6. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 2 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.	Each Nexium™ Delayed-Release Capsule comprises a pharmaceutical composition comprising 44.5 mg or 22.30 mg esomeprazole magnesium trihydrate (40 mg and 20 mg esomeprazole), a compound within the scope of claim 2 that is present in an amount that inhibits gastric acid secretion, and at least one pharmaceutically acceptable carrier. Nexium™ Delayed-Release Capsules are therefore within

Applicable Claims of U.S. Patent No. 4,738,974	Manner in Which Each Claims Reads on Approved Product (Nexium™ Delayed-Release Capsules) or a Method of Using the Approved Product
	the scope of claim 6.
8. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound according to claim 4 in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier.	Each Nexium™ Delayed-Release Capsule comprises a pharmaceutical composition comprising 44.5 mg or 22.30 mg esomeprazole magnesium trihydrate (40 mg and 20 mg esomeprazole), a compound within the scope of claim 4 that is present in an amount that inhibits gastric acid secretion, and at least one pharmaceutically acceptable carrier. Nexium™ Delayed-Release Capsules are therefore within the scope of claim 8.
9. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 1 sufficient to inhibit gastric acid secretion.	Esomeprazole magnesium is a compound within the scope of claim 1. A method of using esomeprazole magnesium is therefore within the scope of claim 9.
10. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 2 sufficient to inhibit gastric acid secretion.	Esomeprazole magnesium is a compound within the scope of claim 2. A method of using esomeprazole magnesium is therefore within the scope of claim 10.
12. A method for inhibiting gastric acid secretion by administering to mammals an amount of a compound as defined in claim 4 sufficient to inhibit gastric acid secretion.	Esomeprazole magnesium is a compound within the scope of claim 4. A method of using esomeprazole magnesium is therefore within the scope of claim 12.
13. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 1 sufficient to treat gastrointestinal inflammatory disease.	Esomeprazole magnesium is a compound within the scope of claim 1. A method of using esomeprazole magnesium is therefore within the scope of claim 13.
14. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in claim 2 sufficient to treat gastrointestinal inflammatory disease.	Esomeprazole magnesium is a compound within the scope of claim 2. A method of using esomeprazole magnesium is therefore within the scope of claim 14.
16. A method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals an amount of a compound as defined in	Esomeprazole magnesium is a compound within the scope of claim 4. A method of using esomeprazole magnesium is therefore within the scope of claim 16.

Applicable Claims of U.S. Patent No. 4,738,974	Manner in Which Each Claims Reads on Approved Product (Nexium™ Delayed-Release Capsules) or a Method of Using the Approved Product
claim 4 sufficient to treat gastrointestinal inflammatory disease.	
17. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 1 sufficient to provide gastrointestinal cytoprotective effects.	Esomeprazole magnesium is a compound within the scope of claim 1. A method of using esomeprazole magnesium is therefore within the scope of claim 17.
18. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 2 sufficient to provide gastrointestinal cytoprotective effects.	Esomeprazole magnesium is a compound within the scope of claim 2. A method of using esomeprazole magnesium is therefore within the scope of claim 18.
20. A method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals an amount of a compound as defined in claim 4 sufficient to provide gastrointestinal cytoprotective effects.	Esomeprazole magnesium is a compound within the scope of claim 4. A method of using esomeprazole magnesium is therefore within the scope of claim 20.

EXHIBIT D

CHRONOLOGIES OF SIGNIFICANT ACTIVITIES
NDA 21-153; NDA 21-154

NDA 21-153: Chronologies of clinical trials and major communications between the applicant and the FDA from July 18, 1997, to February 20, 2001.

Application #	Date	Description
	May 20, 1997	Submitted a background package for the Pre-IND conference to be held on July 1, 1997.
IND 53,733	Jul. 17, 1997	Sponsor submitted minutes of meeting for the pre-IND meeting held on July 1, 1997.
IND 53,733	Jul. 18, 1997	Submitted Original IND
IND 53,733	Aug. 01, 1997	Received FDA's minutes of meeting for the pre-IND meeting held on July 1, 1997.
IND 53,733	Sep. 18, 1997	Submitted Amendment #1 to Protocol 172 (originally submitted in IND) Submitted the following five new protocols and their corresponding Amendment: 173, 174, 177, 178 and 179.
IND 53,733	May 19, 1998	Submitted protocol 201
IND 53,733	Jul. 15, 1998	Submitted a background package for the Pre-NDA meeting to be held on September 24, 1998.
IND 53,733	Oct. 13, 1998	Received FDA's minutes of meeting for the pre-NDA meeting held on September 24, 1998.
IND 53,733	Nov. 03, 1998	Sponsor submitted minutes of meeting for the pre-NDA meeting held on September 24, 1998.
IND 53,733	Jan. 15, 1999	Submitted the following protocols: 222, 225 and 226
IND 53,733	Jun. 18, 1999	Submitted a background package for the Pre-NDA CMC meeting to be held on September 9, 1999.
IND 53,733	Nov. 10, 1999	Sponsor submitted minutes of meeting for the pre-NDA CMC meeting held on September 09, 1999.
NDA 21-153	Dec. 3, 1999	Submitted New Drug Application.
NDA 21-153	Jan. 5, 2000	Letter from FDA issuing the PDUFA dates for NDA review: 10-month date, Oct. 3, 2000 and 12-month date, Dec. 3, 2000.
NDA 21-153	Jan. 31, 2000	Clinical Amendment to NDA 21-153 that contained Clinical Study Report 222

Application #	Date	Description
NDA 21-153	Feb. 4, 2000	NDA was officially filed for review.
IND 53,733	Apr. 3, 2000	Received FDA's minutes of meeting for the pre-NDA CMC meeting held on September 09, 1999.
NDA 21-153	Apr. 3, 2000	Submitted 4-Month Safety Update Report, and the following amendments to NDA 21-153 were included: Items 2, 3,4,5,6,8,11, 12 and 13.
NDA 21-153	Apr. 27, 2000	Submitted the Pediatric Development Plan for Nexium
NDA 21-153	Jul. 17, 2000	CMC Amendment: a change in the specifications for H 199/18 Magnesium Trihydrate substance (esomeprazole magnesium)
NDA 21-153	Aug. 2, 2000	NDA Amendment: submitted revisions to the draft package insert.
NDA 21-153	Aug. 25, 2000	CMC Amendment: revised drug master file letter of authorization for DMF 1941
NDA 21-153	Sep. 26, 2000	FDA issued deficiency letter citing the need for additional information for the Chemistry section.
NDA 21-153	Oct. 3, 2000	Received approvable letter
NDA 21-153	Oct. 4, 2000	FDA issued the approvable labeling
NDA 21-153	Oct. 6, 2000	NDA Amendment: partial response to October 3, 3000 approvable letter
NDA 21-153	Oct. 13, 2000	CMC amendment: Responded to the FDA's CMC Discipline Review Letter dated September 26, 2000
NDA 21-153	Oct. 16, 2000	AZ submitted complete response to October 3, 2000 approvable letter and requested a meeting to discuss labeling issues.
NDA 21-153	Oct. 26, 2000	FDA notifies AZ that the Class I Resubmission User Fee date is December 20, 2000.
NDA 21-153	Nov. 29, 2000	CMC discipline review letter (second)
NDA 21-153	Dec. 20, 2000	CMC Amendment: Response to Chemistry Discipline Review Letter (dated Nov. 29, 2000)
NDA 21-153	Feb. 20, 2001	FDA issued approval letter for NDA 21-153.

NDA 21-154: Chronologies of clinical trials and major communications between the applicant and the FDA from November 21, 1997, to February 20, 2001.

Application #	Date	Description
	Sep. 16, 1997	Submitted a background package for the Pre-IND conference to be held on October 07, 1997.
	Oct. 31, 1997	Received FDA's minutes of meeting for the pre-IND meeting held on October 07, 1997.
IND 54,599	Nov. 21, 1997	Submitted Original IND (included Protocol 191)
IND 54,599	Dec. 17, 1997	Submitted Protocols 192 and 193.
IND 54,599	May 19, 1998	Submitted Amendment 01 for Protocols 191, 192, and 193.
IND 54,599	Jul. 29, 1998	Submitted a background package for the Pre-NDA meeting to be held on October 19, 1998.
IND 54,599	Dec. 03, 1998	Received FDA's minutes of meeting for the pre-NDA meeting held on October 19, 1998.
IND 54,599	Dec. 21, 1998	Sponsor submitted minutes of meeting for the pre-NDA meeting held on October 19, 1998.
NDA 21-154	Feb. 28, 2000	Submitted New Drug Application.
NDA 21-154	Apr. 5, 2000	NDA was officially filed for review.
NDA 21-154	Apr. 5, 2000	Letter from FDA issuing the PDUFA dates for NDA review: 10-month date, Oct. 3, 2000 and 12-month date, Dec. 3, 2000.
NDA 21-154	Dec. 15, 2000	Received approvable letter
NDA 21-154	Dec. 19, 2000	Response to Nexium approval letter
NDA 21-154	Jan. 29, 2001	FDA notifies AZ that the Class I Resubmission User Fee date is February 20, 2001.
NDA 21-154	Feb. 20, 2001	FDA issued approval letter for NDA 21-154.